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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,177	LEVY, ANDREW P.	
	Examiner	Art Unit	
	Jeanine A. Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,12-15,17 and 26-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,12-15,17 and 26-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/06; 5/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed September 5, 2006. Currently, claims 1, 3, 12-15, 17, 26-28 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 7, 2007 has been entered.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Election/Restrictions

4. Applicant's election without traverse of Group II, Claims 1-5, 12-19, 26-28 in the paper filed November 28, 2005 is acknowledged.

The response to the restriction is made with traverse. The response asserts that upon allowance of the linking claims, the restriction requirement as to the linked inventions shall be withdrawn. This argument has been thoroughly reviewed and deemed persuasive. Upon allowance of a linking claim, the withdrawn claims which are linked by the linking claim will be rejoined.

Claims 6-11, 20-25, 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 6-11, 20-25, 29 drawn to an invention nonelected with traverse in the paper filed November 28, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 3, 12-15, 17, 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of determining a potential of a diabetic patient to benefit from anti oxidant therapy for treatment of a cardiovascular complication by determining a haplotype phenotype of the diabetic patient and thereby determining the potential of the diabetic patient to benefit from said anti-oxidant therapy.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the art

The art teaches Cardiovascular disease includes stroke (N England J. Med, Vol. 349, pages 60-72, 2003). The art defines Cardiovascular disease as the class of diseases that involve the heart and/or blood vessels (arteries and veins). Cardiovascular complications encompasses Aneurysms, Angina, Arrhythmia, Athersclerosis, Cardiomyopathy, Congenital Heart Disease, Congestive Heart Failure, Myocarditis, Valve Disease, Coronary Artery Diseae, Dialated Cardiomyopathy,

Diastolic Dysfunction, Endocarditis, High Blood Pressure(Hypertension), Hypertrophic Cardiomyopathy, Mitral Valve Prolapse, Myocardial Ischemia

The art teaches the effect of vitamin therapy on the progression of coronary artery atherosclerosis varies by haptoglobin type in postmenopausal women (Levy et al. Diabetes Care, Vol. 27, No. 4, pages 925-930, April 2004). Levy teaches that changes in the MLD as a function of haptoglobin phenotype and vitamin therapy were analyzed. The analysis of changes in LDL and HDL levels with and without vitamin therapy were analyzed in diabetic patients. The LDL levels in Diabetic patients was not significantly different between vitamin and placebo treated (see Table 4). Levy asserts that the benefit of antioxidant therapy with vitamin CX and E on progressive coronary artery stenosis may be restricted to woman with the Hp 1-1 phenotype 9page 927, col. 3).

Levy (Diabetes Care, Vol. 27, No. 11, pages 2767, November 2004) teaches "the absence of any statistical interaction indicates that these data do not support the hypothesis that the effects of vitamin E differed by Hp phenotype. Therefore, the results noted above in Hp 2-2 diabetic individuals demonstrating a significant reduction in CV death and myocardial infarction could be spurious and clearly require prospective testing in future trials." Thus Levy teaches the HOPE study cannot be relied upon, but rather replication is advised.

Levy (Pharmacology & Therapeutics, Vol. 112, pages 501-512, 2006) teaches atherosclerotic cardiovascular disease (CVD) was studied in determining whether antioxidant vitamin therapy may or may not be beneficial for a given patient with diabetes. Levy teaches there are a variety of antoxidants (vitamin E, vitamin C, folate, beta carotene, selenium, Q-10). Levy teaches vitamin E reduced CVD death and myocardial infarction in Hp 2-2 DM individuals in the HOPE study. However, no benefit was found from vitamin E supplementation in the diabetic cohort alone (page 510, col.

2). Levy teaches that there was no benefit observed in Hp 1-1 or Hp 2-1 individual with DM. Further, the WAVE and HPS studies did not find any benefit associated with antioxidant vitamin in the Hp 2 DM population. Levy suggests a 4-year double blinded clinical trial with 1500 Hp 2-2 DM individuals is being conducted in order to try to validate the findings presented above for Hp 2-2 DM individuals. Thus, it is clear that a single study show narrow results, but the results were not replicated in two additional studies.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

Guidance in the Specification and Working Examples

The specification provides no evidence that the broad scope of the claims are enabled. The specification has analyzed vitamin E and Ramipril which are deemed to be two particular anti-oxidant therapies. The specification teaches there is a 100% concordance between the haptoglobin phenotype as determined from plasma and the haptoglobin genotype as determined from genomic DNA by the PCR. As seen in Table 5 of the instant specification (page 45), the analysis based on DM patients only did not provide a statistically significant result for Hp 2-2 phenotype for stroke when treated with vitamin E. Table 6 illustrates that in diabetic patients the Hp 2-2 phenotype is not associated with CV death, MI or Stroke. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention as broadly as claimed.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

The claims are broadly drawn to any cardiovascular complication, however, the specification fails to provide a significant association between CV, MI or stroke. Given the guidance in the instant specification it is clear that the skilled artisan would not be able to use the presence of the Hp 2-2 phenotype as indicative of CV, MI or stroke. The non-significant p-values provided for the analysis in the specification do not support a method for determining a potential of a diabetic patient to benefit from oxidant therapy. While the skilled artisan could provide additional experimentation to determine whether a subgroup of the population, or another population may have an association

between hp 2-2 phenotype and all cardiovascular diseases, the results are unpredictable, since three of the four complications studied did not yield positive associations. The extremely large number of cardiovascular complications combined with the negative teachings for the analyzed complications would require the skilled artisan to perform unpredictable experimentation to determine whether a predictable correlation exists.

Furthermore, given the analysis in the specification of vitamin E and Ramipril, there is no predictable correlation between Hp 2-2 phenotype and greater benefit for anti oxidant therapy. Diabetic patients with CV death and MI appear to be significantly associated with vitamin E. However, diabetic patients provided Vitamin E showed no association with stroke. The association pattern for Ramipril is different. CV death, MI and Stroke each do not appear to be significantly associated with Hp 2-2 phenotype in diabetics. Based upon the different patterns, the administration of one anti-oxidant therapy would not be indicative of each other anti-oxidant therapy. For example, since Vitamin E and Ramipril each have different associations, it would unpredictable whether Vitamin C, for example, would be associated with anti oxidant therapy benefits. The specification does not provide any analysis for diabetic retinopathy, nephropathy or neuropathy, for example. Therefore, it would be unpredictable whether either Vitamin E, Vitamin C or Ramipril would be associated with Hp 2-2 phenotype and benefits from anti-oxidant therapy.

Moreover, the study, as reviewed by Levy (2006) appears to be only one of 3 studies that was performed. No replication of the data was obtained in the additional studies in the WAVE or and HPS studies. The WAVE and HPS studies did not find any benefit associated with antioxidant vitamin in the Hp 2 DM population. In fact Levy suggests a 4-year double blinded clinical trial with 1500 Hp 2-2 DM individuals is being

conducted in order to try to validate the findings presented above for Hp 2-2 DM individuals. Furthermore, Levy (Diabetes Care, Vol. 27, No. 11, pages 2767, November 2004) teaches "the absence of any statistical interaction indicates that these data do not support the hypothesis that the effects of vitamin E differed by Hp phenotype. Therefore, the results noted above in Hp 2-2 diabetic individuals demonstrating a significant reduction in CV death and myocardial infarction could be spurious and clearly require prospective testing in future trials." Thus, the art clearly teaches the need for replication and reliability.

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the specification and the art do not provide a reliable association between anti oxidant therapies and benefits to cardiovascular complications in diabetic patients. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems for association studies. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it

is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts that the amendments to the claims overcomes the rejection. This argument has been considered but is not convincing because the specification teaches a lack of association in several cardiovascular conditions, including CV, MI or stroke. The response asserts that cardiovascular complication is intended to refer to complications involving the heart, and exclude stroke. This argument has been reviewed but is not convincing. The prior art associates stroke as a cardiovascular complication. The arguments provided by the attorney may not be used to limit the scope of a claim.

The response asserts that the correlation is established in the specification in Table 5. This argument has been reviewed but is not convincing. The claims are specifically drawn to diabetic patients. Table 5 is directed to both all patients and DM patients. Regardless, there are no significant values in the specification for "all patients". All of the p-values are NS. Thus, no correlation exists. Moreover, looking at DM patients only two significant values exist for vitamin E and CF death and MI. As discussed above, these two particular cardiovascular complications are not representative of the full breadth of the claims. Cardiovascular complications encompasses Aneurysms, Angina, Arrhythmia, Athersclerosis, Cardiomyopathy, Congenital Heart Disease, Congestive Heart Failure, Myocarditis, Valve Disease, Coronary Artery Diseae, Dialated Cardiomyopathy, Diastolic Dysfunction, Endocarditis,

High Blood Pressure(Hypertension), Hypertrophic Cardiomyopathy, Mitral Valve Prolapse, Myocardial Ischemia. It is unpredicatable which complications are and which complications are not associated.

The response asserts that ramipril is correlated with primary complications in DM patients. The data in Table 6 illustrates that CV death, MI and stroke are not associated with ramipril administration (page 46).

The response asserts that Blum showed that diabetic mice carrying the haptoglobin 2 variant were more susceptible to MI as well as being significantly benefited by antioxidant treatment. The response notes the data was not conducted in humans. This argument has been reviewed but is not persuasive. As applicants correctly point out, the data is performed in mice. Blum pointed out several limitations of their study.

> This study has several limitations. First, although overall the total number of mice used was consistent with other transgenic studies using the IR model, a few of the measurements in this study relied on a small number of mice. Second, the Hp 2 allele does not normally exist in mice and may have resulted in physiologic changes that we have not measured. Third, it is not possible to know whether the associations that we have observed are specific to DM because we have not studied the described associations in these mice in the absence of DM. Finally, we have not directly demonstrated that the protective effects of BXT-51072 were mediated by its antioxidant action or by some other unknown mechanism.

Given the significant limitations of the study provided by Blum, further experimentation would be required prior to correlating the data to humans, and concluding that the BXT-51072 were the protective antioxidant action.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

7. No claims allowable.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

Jeanine Goldberg
Primary Examiner
May 23, 2007